

Influence of Physical Parameters and Lubricants on the Compaction Properties of Granulated and Non-granulated Cross-linked High Amylose Starch

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Cross-linked high amylose starch (CLA) is a pharmaceutical excipient used in direct compression for the preparation of controlled release tablets and implants. In this work the compression properties of CLA in bulk and granulated forms (without binder) were evaluated for the first time. Tablets were prepared on an instrumented single punch machine. The flow properties and the compression characteristics (compressibility, densification behavior, work of compression) of the materials as well as the mechanical strength of the finished compacts (compactibility) were systematically examined. Wet granulation was found to improve the flowability and the compressibility of CLA but concomitantly reduced its compactibility. It was demonstrated that CLA was a plastically deforming material with a plasticity index and a yield pressure value comparable to those of pregelatinized starch. The compactibility of granulated CLA was independent of particle size in the range of 75 to 500 μm , but slightly decreased when the percentage of the fine particles (<75 μm) in the bulk powder was increased. Water and colloidal silicone dioxide facilitated the consolidation of CLA, while magnesium stearate had an opposite effect on the tablet crushing force.

Key words contramid; cross-linked starch; matrix tablets; direct compression; controlled released; compaction behavior

Starch and its derivatives have been used in a variety of pharmaceutical formulations, including topical and ophthalmic preparations, film-coated tablets, capsules and compressed matrix systems.^{1–4} Biodegradable matrices made from polysaccharides such as starch are particularly interesting in drug delivery because their degradation products occur naturally in the human body. More recently, cross-linked high amylose starch (CLA) has been introduced, under the trademark of Contramid[®], as a controlled release excipient for the preparation of solid dosage forms.⁵ CLA is pregelatinized phosphate cross-linked hydroxypropylstarch containing 70% amylose and 30% amylopectin. Until now, CLA matrices have been mainly prepared by direct compression⁶ of the drug/polymer physical mixture but the influence of physical parameters on the compression properties of this material have never been addressed. It is recognized that the preparation of tablets requires good powder flowability and compactibility.⁷ A good flowability permits rapid and uniform die filling, while a high compactibility is necessary to ensure formation of tablets with sufficient strength. Flowability and compactibility are generally affected by the powder characteristics such as particle size, size distribution, particle shape, moisture content and by the material properties such as degree of crystallinity, elastic modulus, surface energy and plasticity. Additives such as magnesium stearate (MgSt) and colloidal silicone dioxide (CSD) have been reported to dramatically affect powder flowability and compactibility of certain pharmaceutical excipients, especially those known to deform plastically.^{8–10}

The mechanical properties of starch are well documented in the literature.^{11–14} It has been reported that pregelatinized starch, which is produced by heating an aqueous slurry of starch, followed by a thermic dehydration process⁴ (e.g.

spray-drying, drum-drying or extrusion), has good compression properties and deforms mainly plastically.^{11–14} The plasticity of starch was found to be dependent on particle size, size distribution, particle shape, moisture content and compaction speed.^{8,15} Also, starch is extremely sensitive to the softening effects of alkaline stearate lubricants and thus, it has a high strain sensitivity index.¹⁶ At high strain rates during compaction, a large proportion of the deformation is elastic and hence, relaxation of the tablet occurs during the ejection phase, inducing capping.¹⁷

Over the past 10 years, CLA and CLA matrices have been extensively characterized in a number of studies.^{18–21} However, the compaction properties of CLA have never been studied in detail. CLA is a chemically modified starch that may exhibit a consolidation behavior different from that of pregelatinized starch. Accordingly, the aim of this work was to investigate the compaction properties of CLA powder and its dependence on particle size, size distribution, granulation process, moisture content, dwell-time of applied pressure and presence of additional excipients.

Experimental

Materials Cross-linked high amylose starch (CLA, Contramid[®]) was supplied by Cerestar (Haubourdin, France). Magnesium stearate (MgSt), purchased from Street Chemicals & Co. (Montreal, Canada), and colloidal silicon dioxide (CSD, Cab-O-Sil), purchased from Cabot Corp. (Tuscola, IL), were used as lubricant and glidant, respectively.

Methods. 1) **Granulation of CLA** CLA was granulated without binder using deionised water in a ribbon blender (Marion[®], Chicago, IL) or a high shear granulator (Diosna[®], Osnabrueck, Germany). For the ribbon blender, CLA (16 kg) was stirred in the granulator for 5 min. Then, deionised water (2.4 l) was sprayed at a rate of 250 ml/min under continuous mixing. The granulated CLA (Gr-RB) was further mixed for 5 min and then dried in an air convection oven (Despatch, Minneapolis, MN, U.S.A.) at 50 °C to a final moisture content of 11 ± 1% (w/w). For the high shear granulator, CLA (5 kg) was stirred in the granulator for 5 min at low speed, then

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deionised water (750 ml) was added at a rate of 120 ml/min. A granulation time of 10 min and an impeller speed of 500 rpm were chosen. The granulated CLA (Gr-HS) was dried in a fluid bed (GPCGI Glatt®, Dresden, Germany) for 60 min at 50 °C (inlet temperature). The final moisture content of Gr-HS CLA was 11 ± 1% (w/w). Dry granules were milled using a Quadro Comil® (Quadro Engineering Corporation, ON, Canada) and sieved through a 30-mesh screen.

2) Moisture Content Moisture content in the material was determined by thermogravimetry using a moisture content analyzer (Sartorius MA30, Edgewood, NY, U.S.A.). About 500 mg of the material were heated at 105 °C for 12 min and the change in weight was recorded with a precision of 10 µg.

3) Sorption Isotherm of CLA Sorption isotherm of granulated CLA was determined as follows: samples of 10 g of Gr-HS CLA were equilibrated at 20 °C in desiccators above saturated salt solutions, for at least 3 d. Then, the moisture content of the material was assessed on three 500 mg samples. The relative humidity generated by the saturated salt solutions ranged between 10 and 92%.

4) Densities The true density (ρ) was measured in triplicate by the compression method. The volume of the compact at porosity zero was determined from the force-displacement plot by extrapolating the compaction pressure to infinite.²² Bulk (ρ_b) and tap (ρ_t) densities were determined in triplicate in weighed 250 ml cylinder using an Autotap volumenometer (Quadro Chrome, Boynton Beach, FL, U.S.A.), according to the European Pharmacopoeia. The compressibility index²³ (CI) was calculated using the bulk and tapped densities, according to Eq. 1:

$$CI = \frac{100(\rho_t - \rho_b)}{\rho_b} \quad (1)$$

5) Flow Rate The flow rate (v) was measured according to the European Pharmacopoeia using a PharmaTest® Flow Tester (Hainburg, Germany). About 110 g of CLA powder was carefully poured into a stainless steel funnel. It was stirred at 15 rpm with a conical wire mixer installed in the funnel to avoid the powder-wall friction. The flow rate was measured from the time needed for 100 g of powder to pass through a funnel having a 15-mm aperture. The flow rate measurements were done in triplicate.

6) Preparation of Materials Prior to its use, the non-granulated CLA powder was sieved through a 30-mesh screen to remove large aggregates. For one experiment, Gr-HS CLA was divided into four size fractions (<75, 75–150, 150–250 and 250–500 µm) using a set of standard sieves in an Octagon 2000 type vibratory sieve (Endecott, London, England). Binary mixtures of CLA–CSD (99.75:0.25, 99.5:0.5 w/w) and CLA–MgSt (99.75:0.25, 99.5:0.5 w/w) were prepared by physically mixing the two excipients in a Turbula® mixer (Basel, Switzerland) for 10 and 5 min, respectively. In another series of experiments, Gr-HS CLA was sieved through a 400-mesh screen to remove the fraction of Gr-HS fine particles (<75 µm), then different mixtures of CLA composed of fractions >75 µm (CLA_{>75}) and <75 µm (CLA_{<75}) at proportions of 95:5, 90:10, 80:20, 70:30 and 50:50 (w/w) were prepared.

7) Tablet Preparation Tablets were produced using an instrumented eccentric machine (Korsch EK-O, Berlin, Germany) equipped with force and displacement transducers for both punches, as previously described by Rime *et al.*²⁴ The compacts were prepared by manually introducing into a 12-mm die cavity, an exact weight of CLA or CLA-excipient mixture to obtain a 2-mm thick tablet at zero theoretical porosity. The powder bed was then compressed at 150 MPa using flat faced punches. A second compression cycle was performed on the same compact in order to evaluate the plastic component of the densification stage.^{25,26} After the first compression cycle, the compact was pushed back into the die and a second compression was performed.

In addition, to assess the influence of dwell-time on crushing force of CLA compacts, flat faced tablets were prepared at a fixed pressure 150 MPa using a hydraulic laboratory press (Model C, Carver Inc., Wabash, IN, U.S.A.). About 410 mg of CLA were introduced into a 12.9-mm diameter die cavity to produce a 2-mm thick tablet at zero theoretical porosity. The movement of the press was set manually and dwell times of 1, 5, 10 and 20 s were tested.

8) Compression Data Analysis Work calculation (input work, apparent net work, elastic work), plasticity index (PI) and friction parameters such as lubrication ratio (R) and energy of friction (E_{FR}) were determined from the force-displacement data recorded during the compression cycle, as described by Doelker.²⁷ Elastic recoveries (ER) of the tablets, which characterize the relaxation of the compact, were calculated according to Armstrong and Haines-Nutt²⁸ immediately after ejection and 24 h later. ER was expressed

as percent increase in tablet thickness relative to the thickness in the die at maximum pressure. Densification behavior of CLA was evaluated by interpreting data from the continuous recording of a single run by means of the Heckel equation²⁹ (Eq. 2):

$$\ln(1/(1-D)) = KP + A \quad (2)$$

where D is the relative density of the compact, calculated from its dimension under applied pressure P , and K and A are constants. A plot of $\ln(1/(1-D))$ versus P is referred to as a Heckel plot. The constant K and A are the slope and the intercept, respectively, and are calculated from the linear portion of the plot, using a linear regression analysis. The reciprocal of the slope ' K ' is referred to as the mean yield pressure P_y of the powder, while the intercept ' A ' is the sum of two densification terms:

$$A = \ln(1/(1-D_0)) + B \quad (3)$$

where D_0 is the initial relative density of the powder bed and B is a constant related to the densification due to slippage and rearrangement of fragmented particles. Constants A and B can be expressed as relative densities using:

$$D_A = 1 - e^{-A} \quad (4)$$

$$D_B = D_A - D_0 \quad (5)$$

where D_B is the relative density of the powder bed due to fragmentation (see reference²⁷) for more details.

9) Tablet Characterization Thickness and diameter of the tablets were measured with an electronic digital micrometer (Max-Cal, Tokyo, Japan) immediately after ejection, and after 24 h. Tablet porosity (ϵ) was calculated from tablet dimension and powder density. The diametral crushing force (F_c) of the compact was measured 24 h after ejection with a Schenk-Trebel RM 50 mechanical testing machine (Rattinger, Germany) at a cross-head speed of 3 mm/min.

10) Scanning Electron Microscopy CLA powder (non-granulated and granulated Gr-HS) and the internal surface of the fractured tablets were examined by scanning electron microscopy (SEM) (JSM-840, Tokyo, Japan). The samples were fixed on the holder with a liquid adhesive, coated with a thin layer of gold using an ion sputter and then examined by SEM at an accelerating voltage of 10 kV.

11) Statistical Analysis Statistical analysis were performed using ANOVA test and differences were considered statistically significant for p values < 0.05.

Results

Characterization of the Materials

The scanning electron micrographs of non-granulated and granulated CLA (Gr-HS) powder (Figs. 1A, B) show collapsed particles with a polydisperse size distribution and rounded shape. The granulated powder seems to be composed of a few agglomerated particles, and the surface of the individual particles is relatively smooth and non-porous.

The size distribution of granulated CLA powder is presented in Fig. 2. Gr-HS and Gr-RB followed a log-normal modal distribution pattern with a geometric mean particle size of 135 µm and 90 µm, respectively. The fraction of particles smaller than 75 µm was significantly higher in Gr-RB (62%) than in Gr-HS (48%) CLA. Moisture content, true density, bulk density, tapped density, flow rate and compressibility index of granulated and non-granulated CLA are reported in Table 1. The moisture content of all powders was quite close, ranging between 9 and 11%. Granulated CLA had higher values of bulk and tapped densities and was less compressible (lower values of compressibility index) than the non-granulated powder. There was no significant difference between the physical characteristics of Gr-HS and Gr-RB CLA, except for the flow rate, which was approximately twice higher for Gr-HS CLA. The true densities ranged between 1.57 and 1.56 g/cm³. These values are comparable to that of pregelatinised starch² (1.55 g/cm³). The effect of particle size on physical characteristics of Gr-HS CLA was also

investigated. Four fractions (<75, 75–150, 150–250, 250–500 μm) of Gr-HS CLA were collected by sieving and characterized (Table 1). The bulk density seemed to slightly increase with the particle size, whereas there was no general trend for the tapped density. The flow rate (expressed in second) and the compressibility index slightly decreased as the particle size increased.

The moisture sorption isotherm of Gr-HS CLA was determined at 20 °C and the results are shown in Fig. 3. Sorption data were fitted to Eq. 6 using a non-linear least-square method. This equation was proposed by Guggenheim *et al.*

and is frequently used to describe sorption of water by starches³⁰:

$$\frac{w}{w_m} = \frac{C_g \cdot K \cdot a_w}{(1 - K \cdot a_w)(1 - K \cdot a_w + C_g \cdot K \cdot a_w)} \quad (6)$$

where w is the amount of sorbed water, w_m is the amount of sorbed water present as a monolayer, a_w is the activity of water in the powder, C_g and K are constants. The value of w_m was found to be 9.3%, which is consistent with the value for pregelatinised starch.^{2,31}

Compression Characteristics. 1) Effect of Granulation Process The ability of CLA to form compacts of a given mechanical strength as a function of compaction pres-

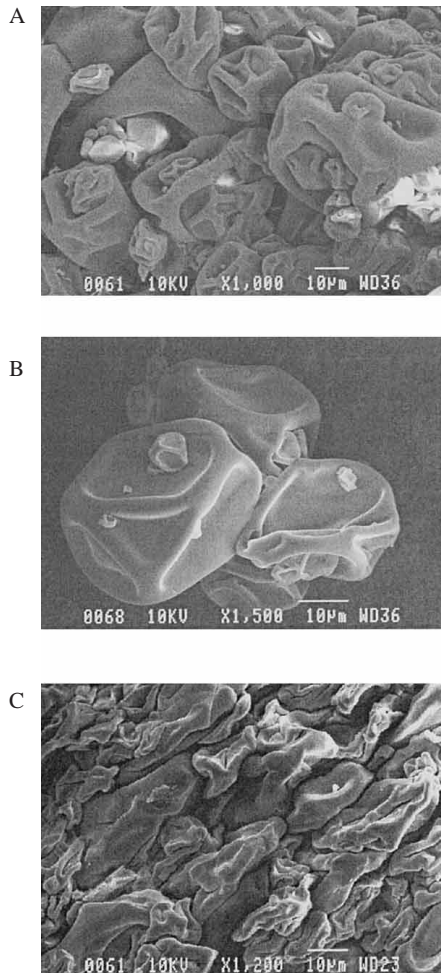


Fig. 1. Scanning Electron Micrograph of Non-granulated CLA (A), Granulated CLA Gr-HS (B) and Internal Surface of Fractured CLA Tablet Compressed at 150 MPa (C)

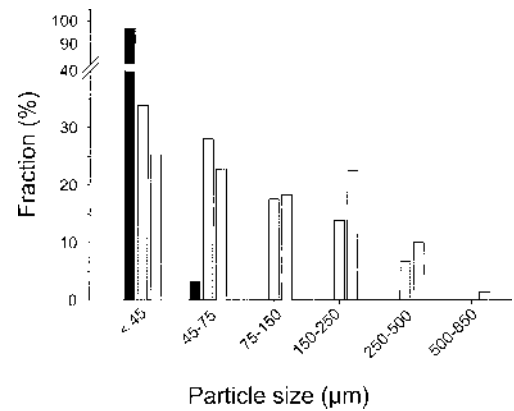


Fig. 2. Particle Weight Size Distribution of Non-granulated CLA (Black Bars) and Granulated CLA, Gr-RB (Shaded Bars) and Gr-HS (White Bars)

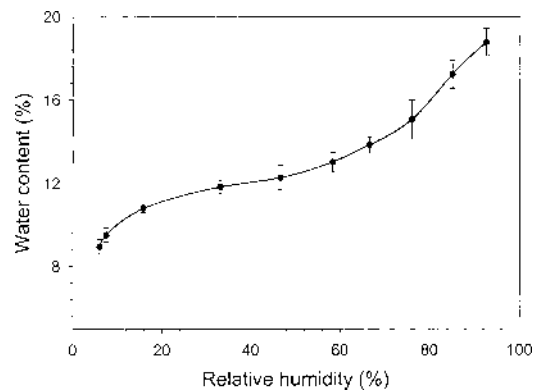


Fig. 3. Water Sorption Isotherm of Gr-HS CLA at 20 °C Mean ± S.D. (n=3).

Table 1. Physical Characteristics of Granulated and Non-granulated CLA

	Moisture content (%)	ρ (g/cm ³)	ρ_b (g/cm ³)	ρ_t (g/cm ³)	v (s)	CI (%)
Ungranulated CLA	9.2	1.56	0.21	0.30	^{a)}	29.1
Granules Gr-HS						
Granules as is	10.6	1.56	0.37	0.48	18.1	22.8
<75 μm		1.57	0.30	0.41	^{a)}	26.7
75–150 μm		1.57	0.32	0.38	11.1	15.8
150–250 μm		1.56	0.34	0.39	7.5	14.0
250–500 μm		1.56	0.35	0.40	5.6	13.0
Granules Gr-RB	11.1	1.56	0.36	0.47	33.2	23.9

For abbreviations consult end of the manuscript. ^{a)} No flow.

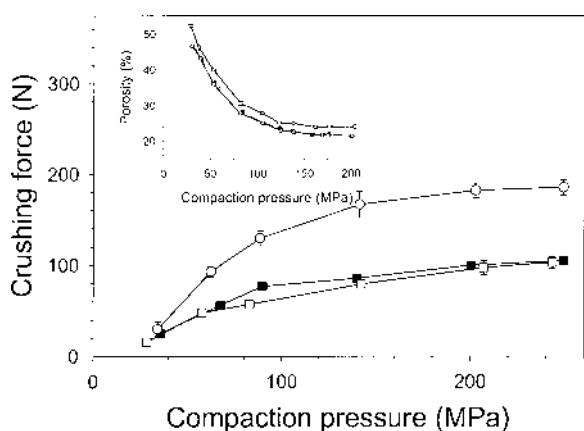


Fig. 4. Compactibility of Non-granulated (Open Circles), Gr-HS (Closed Squares) and Gr-RB (Open Squares)
Inset: Tablet porosity versus compaction pressure (same legend).

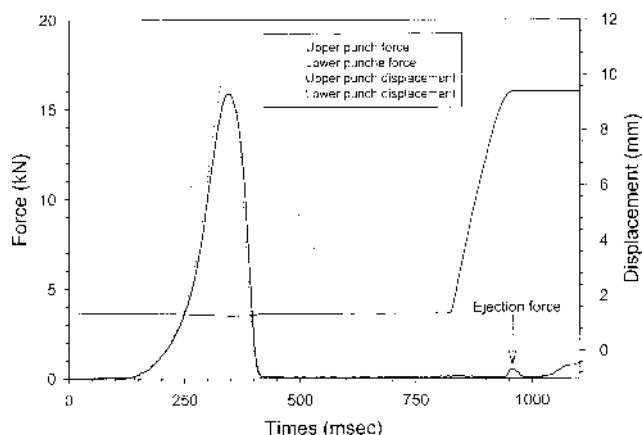


Fig. 5. Typical Compression Force-displacement Profiles of Gr-HS CLA

sure (compactibility) is shown in Fig. 4. As the compaction pressure increased, the diametral crushing force of tablets prepared with granulated CLA increased until a plateau value of approximately 105 N was reached. For the non-granulated CLA, the maximum crushing force was reached at 190 N. The tablet porosities at different compaction pressures are slightly higher for the non-granulated powder. Tablets prepared with the hydraulic press Carver[®] exhibited a compactibility behavior similar to those prepared with the Korsch press. As shown in Table 2, the crushing force of CLA compacts prepared with the Carver press at a compaction pressure around 150 MPa and different dwell-times, ranged between 80 and 86 N, for granulated CLA, and between 178 and 182 N, for non-granulated CLA. The crushing force of these compacts was independent of dwell-time between 1 and 20 s.

Typical force-displacement profiles obtained during the compression cycle of CLA are shown in Fig. 5. Calculated values of the main compression parameters of granulated and non-granulated CLA based on actual profiles are grouped in Table 3. Values of tablet porosity, elastic recovery after ejection and crushing force of the compact are also included in Table 3. The elastic recovery of the compact after 24 h is not presented in this table because further expansion after ejection did not exceed 0.5%. The work required to form a compact at 150 MPa and the friction parameters (lubrication

Table 2. Effect of Dwell Time on the Crushing Force (N) of Granulated and Non-granulated CLA

	Dwell-time(s)			
	1	5	10	20
Non-granulated CLA	181 (9)	179 (9)	178 (5)	182 (10)
Granulated CLA (Gr-HS)	82 (4)	82 (1)	85 (1)	84 (1)
Granulated CLA (Gr-RB)	86 (1)	84 (3)	83 (3)	81 (3)

Tablets were compressed using the hydraulic press at a compaction pressure of 150 MPa. Mean (S.D.), n=3.

Table 3. Effect of the Granulation Process on the Compression Properties and Characteristics of CLA Tablets Prepared at 150 MPa

	Non-granulated	Gr-RB	Gr-HS
E_i (J)	14.5 (0.2)	11.7 (0.2)	11.8 (0.4)
E_{AP} (J)	13.6 (0.1)	10.8 (0.3)	11.0 (0.4)
E_{EXP} (J)	0.8 (0.3)	0.9 (0.2)	0.7 (0.1)
E_{FR} (%)	11.3 (0.7)	7.8 (0.4)	6.8 (1.7)
F_{RES} (N)	229 (30)	73 (9)	69 (10)
F_{EJE} (N)	537 (82)	504 (35)	497 (81)
R (%)	0.81 (0.00)	0.89 (0.03)	0.90 (0.01)
ϵ (%)	25.3 (0.6)	24.3 (0.6)	23.0 (0.0)
ER (%)	20.0 (0.4)	19.4 (0.9)	18.4 (0.4)
P_y (Pa)	82.3 (3.3)	77.2 (10.6)	75.3 (7.1)
PI (%)	71.8 (2.1)	68.7 (2.3)	70.0 (0.3)
F_c (N)	166 (14)	79 (2)	86 (2)

Mean (S.D.), n=3. E_i , input energy of compression; E_{AP} , apparent net energy of compression; E_{EXP} , elastic energy (energy of expansion); E_{FR} , energy of friction; F_{RES} , residual lower punch force; F_{EJE} , ejection force; R , lubrication index; ϵ , tablet porosity; ER, elastic recovery; P_y , yield pressure; PI, plasticity index; F_c , crushing force.

index and energy of friction) involved during the compression phase were significantly higher for the non-granulated powder. However, elastic recovery and tablet porosity remained relatively high after granulation. The yield pressure values (P_y) derived from Heckel plots were relatively low but not statistically different ($p > 0.05$) before and after granulation. The same is true for the plasticity index (PI). The yield pressure is often used to characterize the densification mechanism of powders. Materials with a high yield pressure are classified as brittle or fragmenting materials, whereas those with low values belong to the category of plastically/elastically deforming materials.²⁷⁾ In fact, examination of the scanning electron micrographs of the internal surface of fractured CLA tablets in Fig. 1C showed plastic deformation of the particles. The absence of fragmentation upon compression was confirmed by calculating the critical particle size (d_{crit}) at which the transition from brittle to ductile behavior would occur,³²⁾ (Eq. 7):

$$d_{crit} = (3.27 K_{IC} / P_y)^2 \tag{7}$$

where K_{IC} is the critical stress intensity factor. By taking $K_{IC} = 1.84 \text{ MPa} \cdot \text{m}^{1/2}$ (internal data) and $P_y = 78.3 \text{ MPa}$, a d_{crit} value of 5.9 mm was obtained. The critical diameter of granulated CLA was calculated on rectangular notched beams of dimensions 20 mm long by 7 mm wide and varying height, using a three-point test according to Roberts *et al.*³³⁾ In order to calculate K_{IC} at zero porosity, an exponential relationship was used between K_{IC} and the porosity of the beams.

Another interesting result given in Table 3 is the “self-lubricating” effect of granulated CLA. Despite low ejection

Table 4. Effects of Particle Size and Percentage of Fine Particles on the Compression Properties and Mechanical Characteristics of Gr-HS CLA

	E_1 (J)	E_{FR} (%)	P_y (MPa)	ER (%)	F_c (N)
Fractions (μm)					
<75	12.2 (0.2)	9.1 (0.3)	75.0 (2.0)	18.2 (0.3)	78 (6)
75—150	12.3 (0.3)	8.5 (0.3)	71.5 (5.9)	19.8 (0.6)	85 (1)
150—250	12.5 (0.2)	8.5 (0.4)	71.7 (2.7)	18.8 (0.7)	91 (0)
250—500	13.4 (0.2)	8.8 (0.2)	72.9 (4.4)	20.3 (0.1)	80 (2)
% of fine particles					
0	12.4 (0.2)	8.7 (1.4)	71.0 (2.1)	18.1 (0.2)	98 (2)
5	12.5 (0.1)	10.8 (0.3)	75.2 (4.8)	17.7 (0.2)	96 (2)
10	12.4 (0.1)	11.7 (0.6)	71.0 (0.4)	17.7 (0.2)	93 (3)
20	12.2 (0.2)	11.4 (0.3)	73.3 (0.9)	18.0 (0.3)	90 (2)
50	12.4 (0.2)	11.3 (0.4)	76.8 (4.0)	18.1 (0.4)	84 (2)
75	12.4 (0.1)	12.0 (1.0)	76.9 (0.5)	17.8 (0.1)	72 (3)
100	12.2 (0.2)	11.2 (0.4)	75.0 (2.0)	18.2 (0.3)	78 (6)

Mean (S.D.), $n=3$. For abbreviations see footnote of Table 3.

Table 5. Effect of MgSt and CSD on the Compression Properties and Mechanical Characteristics of Gr-HS CLA

	E_1 (J)	E_{EXP} (J)	E_{FR} (%)	R	ϵ (%)	ER (%)	F_c (N)
No additive	11.8 (0.4)	0.7 (0.1)	6.8 (1.7)	0.90 (0.01)	23.0 (0.0)	18.4 (0.4)	86 (2)
MgSt (%)							
0.25	10.4 (0.1)	0.9 (0.2)	5.1 (0.7)	0.93 (0.01)	24.5 (0.6)	19.3 (0.1)	37 (3)
0.50	10.4 (0.2)	0.9 (0.1)	3.9 (0.1)	0.96 (0.02)	25.3 (0.6)	20.6 (0.2)	26 (1)
SiO ₂ (%)							
0.25	12.2 (0.1)	0.7 (0.1)	10.9 (0.4)	0.82 (0.00)	21.0 (0.0)	15.5 (0.2)	219 (4)
0.50	12.5 (0.3)	0.7 (0.1)	12.0 (0.2)	0.81 (0.00)	20.0 (0.0)	14.8 (0.3)	244 (5)

Mean (S.D.), $n=3$. For abbreviations see footnote of Table 3.

forces measured in absence of lubricant (Table 3), the non-granulated CLA powder was not “self-lubricating”. Its lubrication index R was relatively lower ($R=0.81$) than that of the granulated powder ($R=0.89$ and 0.90 for Gr-RB and Gr-HS, respectively). This is also reflected in the values of friction energy ($E_{FR}=11.3$ for the non-granulated powder versus 7.8 and 6.8 for Gr-RB and Gr-HS, respectively).

2) Effect of Particle Size and Percent of Fine Particles

The effect of particle size and that of percentage of fine particles (smaller than $75 \mu\text{m}$) on the compression parameters and mechanical properties of CLA compacts are reported in Table 4. The work of compaction did not differ for particle size fractions up to $150\text{--}250 \mu\text{m}$, but was slightly higher for the $250\text{--}500 \mu\text{m}$ size fraction. As for elastic recovery of the final compacts after ejection and yield pressure, they were totally independent of particle size. The fragmentation indices derived from the Heckel plots were almost nil for all size fractions (data not shown). The presence of particles smaller than $75 \mu\text{m}$ in Gr-HS CLA had no effect on the work of compaction, the yield pressure, the fragmentation index and the elastic recovery of the final compacts. However, the crushing force of the compacts slightly decreased from 98 to 72 N as the proportion of fine particles increased from 0 to 75% .

3) Effect of Magnesium Stearate and Colloidal Silicone Dioxide

The effect of MgSt and CSD on the compression and mechanical properties of compacts prepared with granulated CLA is reported in Table 5. The results indicate that the presence of MgSt, even at low concentrations, impaired the compactibility of CLA. The crushing force of the compacts containing 0.25% and 0.5% MgSt decreased by 54% and 67% , respectively. This was accompanied by an increase in the elastic recovery and tablet porosity. On the other hand,

the friction parameters were considerably improved in the presence of MgSt. The addition of 0.5% MgSt resulted in a decrease of the friction energy from 6.8 to 3.9 and in an increase of the lubrication ratio from 0.90 to 0.98 . However, neither the ejection force nor the yield pressure were affected by the lubricant (data not shown).

CSD also had a dramatic effect on the compactibility of CLA, but contrary to MgSt, stronger compacts were obtained. As shown in Table 5, the presence of 0.25% and 0.5% CSD lead to a respectively 2.8- and 3.1- fold increase in crushing force, and significantly reduced elastic recovery and tablet porosity. The friction parameters, however, were negatively affected as indicated by an increase of friction energy and a decrease of lubrication index.

4) Effect of Moisture Content The main compression parameters and mechanical properties of compacts made with Gr-HS CLA at different moisture contents are reported in Table 6. Plasticity, tablet porosity and elastic recovery slightly decreased with increasing water content. Work of compaction, apparent net work and friction energy followed the same trend but the decrease was much more pronounced. The work required to form a compact at 5% moisture content was approximately 60% higher than that required at 14% moisture content. The crushing force of the final compacts was significantly affected by water concentration and increased from 34 N (5%) to 128 N (14%). Also, the increase of moisture content lead to a significant decrease in the yield pressure from 94 MPa (5%) to approximately 76 MPa ($11\text{--}14\%$).

Discussion

CLA was recently introduced, under the trademark of Con-

Table 6. Effect of Moisture Content on the Compression Properties and Mechanical Characteristics of Gr-HS CLA

	Moisture content of the powder			
	5%	11%	12.5%	14%
E_I (J)	16.4 (0.3)	11.8 (0.4)	10.9 (0.1)	10.4 (0.1)
E_{AP} (J)	15.4 (0.3)	11.0 (0.4)	9.9 (0.1)	9.7 (0.1)
E_{EXP} (J)	1.0 (0.2)	0.7 (0.1)	1.0 (0.0)	0.7 (0.0)
E_{FR} (%)	11.2 (0.5)	6.8 (1.7)	5.7 (0.9)	5.5 (0.6)
F_{EJE} (N)	483 (51)	497 (81)	447 (73)	457 (87)
R (%)	0.79 (0.00)	0.90 (0.01)	0.93 (0.02)	0.92 (0.01)
ϵ (%)	28.7 (0.6)	23.0 (0.0)	22.3 (0.6)	22.0 (0.0)
ER (%)	20.1 (0.2)	18.4 (0.4)	17.7 (0.5)	17.7 (0.4)
P_y (MPa)	94.1 (1.1)	75.3 (7.1)	77.5 (3.1)	76.2 (0.7)
PI (%)	72.2 (1.1)	70.0 (0.3)	68.4 (0.7)	67.7 (0.8)
F_c (N)	34 (2)	86 (2)	102 (2)	128 (2)

Mean (S.D.), $n=3$. For abbreviations see footnote of Table 3.

tramid[®], as a controlled release excipient for the preparation of solid dosage forms. CLA is prepared by cross-linking of high amylose starch followed by gelatinization and spray drying. The bulk powder cannot be used for direct compression as supplied by the manufacturer because of its poor flowability due to the very small particle size. This powder does not flow through a funnel with a 15-mm aperture and its compressibility index is relatively high (Table 1). The scanning electron micrographs of this powder (Fig. 1A) showed rounded, collapsed particles with a polydispersed size distribution. The surface of these particles appeared relatively smooth and non-porous. They exhibited many small cavities, which can act as sites for preferential accumulation of other powdered substances, thereby promoting the ability to form stable ordered mixtures with little tendency to segregate. Since CLA would constitute a high fraction of most formulations prepared by direct compression, the effect of CLA on the overall flow property of the blend is major. The flow properties of CLA must be considerably improved to obtain a free-flowing powder blend and to counterbalance the usually poor flow characteristics of the other ingredients. A simple method to improve the flowability and compatibility of excipients is to granulate the powder.²²⁾ Two different granulation methods (*i.e.* ribbon blender and high shear granulator) were evaluated in this work. The powder flowability, as measured by the flow rate and compressibility index, was greatly improved by granulation process. This is generally attributed to the increase of particle size, but examination of the scanning electron micrographs of the granulated powder (Fig. 1B) did not show large agglomerates. Granulated CLA exhibited relatively high bulk and tapped densities, and the compressibility index was about 22–24%, which is typical of a fair-passable flowability material.³⁴⁾ The flow rate of Gr-HS CLA was approximately twice higher than that of Gr-RB CLA (Table 1). This difference in flowability may be attributed to particle size. Indeed, Gr-RB CLA presented substantially more particles smaller than 75 μm (Fig. 2). This fraction did not flow through the funnel (Table 1). It is well known that powder flowability is size-dependent, and as particle size increases, the total surface area decreases, resulting in a reduction of friction between particles and hence a better flowability.

Granulation substantially decreased the compactibility of

CLA as indicated by a reduction in tablet strength at equivalent compaction pressure. The reduction of compactibility after wet granulation has been observed for many pharmaceutical excipients and especially plastic materials. This has been attributed to the decrease of the bonding surface area, which can develop intermolecular forces.³⁵⁾ The bonding surface area is often defined as the effective surface area taking part in interparticle attraction and depends mainly on the particle size, particle shape and consolidation mechanism of the powder. Accordingly, larger particles undergoing plastic deformation (see below) are expected to provide less bonding surface area, and thus form weaker tablets. However, the reduction of CLA compactibility following wet granulation should not be entirely attributed to differences in particle size since the crushing force of granulated CLA compacts was barely influenced by particle size (Table 4). It could therefore also be related to the increase in crystallinity during wet granulation. Indeed, Le Bail *et al.*¹⁹⁾ have demonstrated that the crystallinity of CLA, especially the B form, increased when the powder was hydrated. The B crystalline form has been reported to increase the stiffness of starches and decrease their strain at break.³⁶⁾ Moreover, the effect of crystallinity on the compactibility of the powder has been observed for other pharmaceutical excipients such as microcrystalline cellulose,¹⁶⁾ ethylcellulose³⁷⁾ and lactose.^{38,39)}

The compression properties of CLA and its densification behavior were evaluated from the plot of the compression force-displacement data. The results indicate that the non-granulated powder offered much more resistance to consolidation than granulated CLA. A high input energy was required to form compacts with the non-granulated powder. A significant part of this energy was lost by die-wall and interparticle friction, as reflected by the high values of friction energy (E_{FR}) and lubrication index (Table 3). In contrast, the friction parameters after decompression (F_{RES}) and during ejection (F_{EJE}) were relatively low. An opposite trend was observed with granulated CLA. The input energy of compression (E_I), the apparent net energy (E_{AP}) which is permanently imparted to the compact, and the friction energy were significantly lower and their values similar for both granulated powder. The friction energy decreased by approximately 40%, whereas the friction parameter after decompression was reduced by more than 3-fold, when the powder was granulated. However, the elastic energy (E_{EXP}) which is delivered by the compact in the die during the decompression phase and the elastic recovery of the compact after ejection remained rather high for both materials, but were comparable to other common pharmaceutical excipients (*e.g.* hydroxypropylmethylcellulose) used in controlled drug release.¹³⁾

The Heckel plots analysis revealed that CLA deforms plastically. The plasticity indices and the values of yield pressure of granulated and non-granulated CLA were comparable (Table 3). The low value of yield pressure obtained in this study is typical of a plastically-deforming material and is consistent with the yield pressure of pregelatinized starch.^{2,12)} The absence of fragmentation upon compression of CLA is revealed by the low values of the Heckel parameter D_B , which are nil for both materials (data not shown), and was confirmed by the photomicrographs of fractured CLA tablets (Fig. 1C). Moreover, the critical diameter above which the transition from plastic to brittle materials occurs, was calcu-

lated to be 5.9 mm. This value is far beyond the usual particle size of CLA used in direct compression. Another parameter derived from Heckel plots, *i.e.* D_0 , which represents the densification of the powder bed by particle rearrangement before interparticle bonding occurs, was slightly higher after granulation (data not shown). This indicates that wet granulation promoted slippage and rearrangement of particles during the early stage of compression, leading to lower energy of friction and better transmission of the compression force from the upper to the lower punch.

The effect of particle size on the compression properties of Gr-HS CLA was also evaluated. Although the increase in particle size markedly affected the flow rate of CLA, it had a low impact on the compaction mechanisms. The yield pressure values of different GrHS CLA fractions were similar. Indeed, the yield pressure of plastically deforming materials such as starch is independent of particle size.¹²⁾ Although particle size influences particle slippage and rearrangement and, therefore, consolidation, the crushing force of granulated CLA compacts was found to be only slightly affected by granule size. The presence of small particles in powders is known to be an important contribution to the consolidation process of a compound. Small particles can fill the void spaces between the bigger particles leading to increased bonding surface area, hence producing harder compacts. However, an inverse trend was observed with CLA. As the percentage of fine particles ($<75 \mu\text{m}$) of CLA powder increased, the crushing force of the final compacts decreased, while the porosity remained constant (Table 4). This behavior is difficult to explain since the input energy of compaction, the friction parameters and the yield pressure parameter did not change significantly when the % of fine particles increased.

The friction parameters were considerably improved by the addition of MgSt, whereas the ejection force of the compacts was not affected. On the other hand, MgSt was found to dramatically affect the mechanical properties of CLA compacts. Even at low concentrations (0.5%), MgSt caused approximately 70% reduction in tablet strength. It has been reported that MgSt interferes with bonding by formation of a hydrophobic film on the surface of particles during the lubrication process and thus reduces the crushing force of the compacts.^{10,11)} The important decrease in CLA compactibility after lubrication may be attributed in part to particle morphology. Indeed, the rounded shape of CLA particles limits the bonding surface area and is not favourable for mechanical interlocking between particles during compaction.³⁵⁾ Thus, bonding may be easily hindered by the presence of a hydrophobic film. As a matter of fact, the relative insensitivity of microcrystalline cellulose to lubricants, as compared to starch, is mainly due to its irregular particle shape.³⁵⁾ Finally, the sensitivity of CLA to MgSt is also an indication of the absence of particle fragmentation during the consolidation process. It is generally accepted that fragmenting particles are less sensitive to MgSt than plastic deforming materials. This is attributed to the creation of clean particle surfaces after fragmentation.

CSD also had a dramatic effect on the compactibility of CLA powder, but in contrast to MgSt, harder compacts were obtained. The elastic energy and elastic recovery were also lower in the presence of CSD. The magnitude of the crushing

force of compacts with small amounts of CSD (0.25%) was approximately 3-fold greater than that of pure CLA. This is probably due to the glidant action of CSD, which facilitates the densification of CLA. As a result more interparticle bonds can be created during the compression phase. The elastic nature of the material tends to expand the compacts in the axial direction, but this is opposed by the interparticulate bonds formed initially. As a result a fraction of those bonds is destroyed during the decompression phase. It has been reported that, the survival of the interparticulate bonds depends on the elastic nature of the material, and is inversely related to the number of the bonds formed during the compression phase.^{37,40)} Due to its glidant properties, CSD favors the formation of interparticulate bonds during tableting, and thus reduces the elastic component.

Moisture content has been reported to have an important effect on the properties of starch and starch-based formulations.^{2,36,41,42)} The results obtained in this study clearly demonstrate that a significant change in the mechanical properties of CLA tablets occurs with increasing moisture content. It is well known that water acts as an internal lubricant in starches and facilitates their consolidation.^{36,41,42)} Examination of the friction parameters (lubrication index and friction energy, Table 6) revealed that the lubricating action of water on CLA granules reached its maximum for a moisture content of approximately 11%. Based on the sorption isotherm of Gr-HS CLA (Fig. 3), at this moisture content, there is a monolayer of tightly adsorbed water molecules. Water facilitates the consolidation of the powder probably by reducing frictions between particles and between particles and the die wall.

The effect of water on the mechanical properties of CLA compact is not only attributed to its lubrication action, but also to its softening effect. It has been reported that water acts also as plasticizer in starches,^{36,41,42)} reducing therefore their glass transition temperature. The results obtained in this study showed that the yield pressure of CLA slightly decreased when the moisture content increased from 5 to 14%.

Conclusion

Contramid® is a relatively new pharmaceutical excipient consisting of CLA. It is used in matrix formulation for the controlled release of drugs. CLA can be easily granulated with water in a high shear granulator or in a ribbon blender to produce a powder with good flow properties. As reported for many pharmaceutical excipients, wet granulation improves the flowability of CLA but reduces its compactibility. The result obtained in this study also showed that CLA is a plastic-deforming material. The plasticity index and yield pressure parameters were comparable to those of pregelatinized starch, and independent of particle size, % of fine particles, and presence of MgSt or CSD. Finally, water and CSD facilitated the consolidation of CLA while MgSt had an opposite effect on tablet crushing force.

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